Published in final edited form as:
Am J Cardiol. 2012 June 15; 109(12): 1767–1773. doi:10.1016/j.amjcard.2012.02.022.

Relation between Hemoglobin A1c and Outcomes in Heart Failure Patients with and without Diabetes Mellitus

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Abstract

Among patients with diabetes mellitus (DM) in the general population, elevated glycosylated hemoglobin (HbA1c) increases the risk of developing heart failure (HF). However, in patients with established HF, the association of HbA1c level with outcomes is not well established. This study investigated the relation between HbA1c and outcomes in HF patients with and without diabetes. We studied 845 advanced HF patients followed at the Ahmanson-UCLA Cardiomyopathy Center, stratified by presence (n=358) or absence (n=487) of DM and by DM-specific HbA1c quartiles (Q) (Diabetics: Q1≤6.4%, Q2 6.5–7.2%, Q3 7.3–8.5%, Q4≥8.6%; Non-diabetics: Q1≤5.6%, Q2 5.7–6.0%, Q3 6.1–6.5%, Q4≥6.6%). The primary outcomes analyzed were death and death/urgent heart transplantation (Utx). In the cohort with DM, 2-year event-free survival was 61% and 65% for Q3 and Q4 compared to 48% and 42% in Q1 and Q2 (p=0.005). In the cohort without DM, there was no difference in outcomes by HbA1c Q. Risk-adjusted analysis in the diabetic cohort showed significantly increased hazard ratio (HR) of death/Utx in Q1 and Q2 compared to Q4. For every unit HbA1c increase, there was a 15% decreased HR of death/Utx and all-cause mortality (p=0.006 and p=0.036, respectively). In the cohort without DM, multivariable models revealed similar HR among HbA1c Q. In this cohort of patients with advanced HF, higher HbA1c levels were associated with improved outcomes in patients with diabetes. This relationship was not observed in patients without DM. Further investigations into mechanisms underlying the relationship between HbA1c, DM, and survival in advanced HF are warranted.

Keywords

diabetes; heart failure; glycosylated hemoglobin; outcomes

Introduction

Diabetes mellitus (DM) is a common co-morbidity in patients with HF.[1] The prevalence of DM is approximately 25% in stable HF, compared to only 7% in the general population.[2] This relation may in part be due to pathophysiological processes that underlie both HF and

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DM, including similar patterns of neurohormonal activation, endothelial dysfunction, and oxidative stress.[3] A useful marker of glycemic control in diabetic subjects is glycosylated hemoglobin, or HbA1c. Elevated HbA1c is a risk factor for the development of HF in patients with DM, with a 10–15% increased HF risk for every one unit increase in HbA1c.[4] Although DM and elevated HbA1c levels are associated with an increased risk of new-onset HF[2–4], the data regarding HbA1c and outcomes in patients with pre-existing HF has been conflicting.[5–7] This study aimed to re-evaluate the relationship between HbA1c levels and outcomes in a large, well-characterized cohort of advanced HF patients, including patients both with DM and without DM.

Methods

The study population consisted of 845 patients with advanced HF referred to a single university center between January 1, 1999 and July 1, 2010 who had HbA1c measurements recorded within 6 months of referral. The presence of DM was determined by patient self-report and documentation by physician or documentation of treatment with one or more hypoglycemic agents.

Baseline patient characteristics were collected at time of referral; all testing including measurement of HbA1c and other laboratory testing, echocardiography, cardiopulmonary exercise testing, and right-heart catheterization in selected cases were performed within 6 months of initial referral. Patients were further classified into subgroup-specific quartiles (Q) based on HbA1c levels (Table 1). The cohort was analyzed as a whole and by subgroups based on presence or absence of DM.

The end-points evaluated in this study included 1) death or need for urgent heart transplant (Utx, Status 1A) and 2) all-cause mortality, in which all heart transplants (Status IA, IB, and II) were coded as non-fatal events. Ventricular assist device (VAD) placement was not analyzed as a final endpoint, but rather the subsequent heart transplant or death after VAD was considered as the final outcome. Of 42 subjects who received VADs, 24 subsequently received Utx, 5 received non-urgent transplant, and 13 died.

Baseline characteristics were presented as mean ± SD for normally distributed continuous variables, median (interquartile range) for non-normally distributed variables, and percent of total for categorical variables. Statistical methods employed included independent samples t-test, ANOVA, chi-square test, and non-parametric tests for comparison of variables as appropriate. Kaplan-Meier survival curves were calculated at one- and two-year follow-up. Cox proportional hazards regression analyses were used to estimate the hazard ratio (HR) of the endpoints of death/Utx and all-cause mortality.Variables included in the multivariate were patient age, gender, body mass index (BMI), and left ventricular ejection fraction (LVEF). A p value ≤ 0.05 was considered significant. PASW v.19 (IBM corp. Sommers, NY) was used for analyses.

Results

The cohort was 72% men with a mean age of 55 ± 12 years. Patients with NYHA III or IV comprised 78% of the patient population. The mean HbA1c was 6.7 ± 1.4% (range 3.6–14.3%), and mean LVEF was 25 ± 12%. Of the patients in the cohort, 42% (n=358) had DM and 58% (n=487) did not have DM. In the patients with DM, the mean HbA1c was 7.6% (range 4.5 – 14.3%). In those without DM, the mean HbA1c was 6.0% (range 4.4–8.0%). Table 2 shows characteristics of the cohort stratified by presence or absence of DM. Diabetic subjects were older, with higher BMI, but similar LVEF.

Baseline patient characteristics of the total cohort by HbA1c Q are demonstrated in Table 3 and baseline patient characteristics of cohort stratified by HbA1c in the presence or absence of DM are presented in Tables 4 and 5, respectively. In the diabetic cohort, patients with higher HbA1c were younger and had higher BMI, cholesterol, and blood pressure; these trends were not observed in the non-diabetic cohort.

For the total population, there were 123 deaths during the first year of follow-up and 180 total deaths by two years. Of the deaths by two years, congestive HF accounted for 62.2%, whereas 15.6% of deaths were sudden, and 22.2% occurred from unknown or other causes. At two years, 181 patients (21.4%) had received Utx.

In analyzing the total cohort, Q4 (HbA1c ≥7.2%) had the best survival free from death/Utx (Figure 1a), although this relationship was not significant for the endpoint of all-cause mortality (Figure 1b). After adjusting for age, gender, BMI, and LVEF on multivariable analysis, Q1–Q3 compared to Q4 were at higher risk of death/Utx[HR Q1: 1.52 (1.12–2.05) p=0.007, Q2: 1.27 (0.93 – 1.74) p=0.132; Q3 1.54 (1.14–2.07) p=0.005]. Analyzing HbA1c as a continuous variable in a multivariable analysis, for each unit increase in HbA1c there was an 8% decreased risk of death or need for Utx (HR 0.92; 95% confidence interval [CI] 0.84–1.00, p=0.050).

In the cohort with DM, both survival free from death/Utx and overall survival were significantly better in the higher HbA1c Q (Figure 1c, 1d). After multivariate analysis, Q1and Q2 compared to Q4 were at higher risk of death/Utx [HR Q1: 1.74 (1.04–2.92) p=0.036, Q2: 1.86 (1.13–3.07) p=0.015]. Furthermore, on analyzing HbA1c as a continuous variable, for each unit increase in HbA1c in patients with DM, there was an associated 15% decreased risk of death/Utx and a 15% decreased risk of all-cause mortality [HR 0.85 (0.76–0.95) p=0.006 and HR 0.85 (0.74–0.99) p=0.036, respectively]. For patients with DM, we also performed a separate multivariate analysis in which we additionally adjusted for use of the diabetic medications - insulin, metformin, sulfonylureas, and glitazones – in addition to age, gender, BMI, and LVEF. After adjustment for anti-diabetic medicines, Q1 and Q2 remained at a significantly higher risk compared to Q4 [HR Q1: 1.9 (1.1–3.2) p=0.026, Q2: 2.0 (1.2–3.4) p=0.008, Q3: 1.1 (0.6–1.9) p=0.775].

In patients without DM, both primary outcomes tended to be better in Q3 (HbA1c 5.7% – 6.0%); however, this relationship was not statistically significant (Figure 1e, 1f). HbA1c was also not an independent predictor of outcomes on multivariable analysis.

In order to further investigate the relationship between HbA1c levels and outcomes in HF patients with DM, outcomes by deciles of HbA1c were analyzed. Higher HbA1c deciles were, in general, associated with improved outcomes, with both the best survival free from Utx and best overall survival seen in Decile 8 (HbA1c 8.3 – 8.9%). Comparing Decile 8 to Decile 1, survival free from death/Utx was 79.7% and 34.1%, respectively, and overall survival was 83.2% and 53.8%, respectively. Since gender may modify the risk attributable to DM[8,9] we analyzed survival by HbA1c levels in strata of men vs. women; elevated HbA1c was associated with better survival free from Utx in both men and women (data not shown).

Discussion

HF remains a leading cause of death and disability and affects approximately 6 million people in the U.S. DM is common in HF and associated with higher mortality.[9,10] Despite the abundance of evidence linking DM, insulin resistance, and hyperglycemia to impaired functional status and worse outcomes in patients with HF, there is lack of data and guidelines on optimal strategies to manage DM in patients with chronic HF.HbA1c reflects

the prior 2–3 months of glycemic control and is a useful marker for determining long-term glycemia without reference to prandial state.[11] In this cohort of patients with advanced HF, higher HbA1c levels were associated with improved outcomes in patients with DM. These findings may have important implications for patients with HF and DM.

Recent studies in patients with DM at high cardiovascular risk have failed to show a positive effect of intensive glucose control on macrovascular outcomes or mortality.[12]In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, the intensive-therapyarm (goal HbA1c<7%) showed an increase in the overall mortality by 21% which prompted early termination.[13] Potential explanations for the adverse outcomes include increased rates of hypoglycemia, increased use of insulin, and weight gain in the intensive control group.[14] Thus, for patients with cardiovascular disease and DM, glycemic control to HbA1c ≤ 7% is recommendedfor reduction of cardiovascular risk, rather than more intensive glucose control.[14]

Previous studies have investigated the relationship between HbA1c and outcomes in patients with HF.[5–7]In an analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program, a graded positive association between HbA1c and cardiovascular risk was demonstrated.[7]Aguilar et al. found a U-shaped relationship with the best survival in the group with modest glycemic control (HbA1c 7.1–7.8% range). Our cohort significantly differed from the Aguilar cohort, which was comprised mainly of older men at a less advanced stage of HF.[6] In our advanced HF population, and specifically in the diabetic cohort, we did not find a U-shaped or positive correlation between HbA1c and outcomes in diabetic HF patients but rather found an increase in risk above a HbA1c level of approximately 7.2%, similar to our previous findings in a smaller cohort.[5]

The mechanisms of the relationship between higher HbA1c and improved outcomes in this advanced HF population with DM require further study. HbA1c is a measure that reflects the metabolic state of the patient as a whole, and includes factors like hypoglycemia, cachexia, and catabolic stress.[15]These factors could be indicative of protein energy malnutrition and an increased inflammatory response associated with decreasing HbA1c levels and worse clinical outcomes. A recent study of HbA1c levels in a general non-diabetic US population (n=14,099) also found that very low HbA1c levels were associated with increased all-cause mortality.[16] HF is also associated with insulin resistance, neurohormonal activation, and deranged myocardial glucose and fatty acid metabolism,[17] perturbations which may render HbA1c an insufficient marker for glycemia in this patient population. Anti-diabetic medication usage may play a role; in our cohort patients in higher HbA1c Q were more often on metformin and glitazones, known to be projective in HF,[18,19]but also were more often on insulin therapy, which may have adverse effects in HF.[3,10]Lastly, in HF patients traditional risk factors such as obesity, high cholesterol, and high blood pressure – all associated with higher HbA1c – are associated with improved outcomes in patients with HF, a relation often termed “reverse epidemiology”.[20]Thus, one or all of these factors may be contributing to the improved outcomes seen in patients with higher HbA1c in this advanced HF cohort.

We acknowledge potential limitations of this study. This was an observational study and there were baseline differences in the patient population quartiles. Inherent to the study design, there is the possibility of residual, unmeasured confounding variables that may be contributing to the observed results. For example, blood pressure may be contributing to the observed results and its interaction with HbA1c and outcomes in diabetic patients with advanced HF requires further study. In addition, since severely ill patients are more likely to have their HbA1c levels measured and recorded as part of a heart transplant evaluation, the cohort pool may be skewed towards more chronically or acutely ill patients. Furthermore, in

light of recent changes in the American Diabetes Association's guidelines on the diagnosis of DM to include patients with HbA1c levels >6.5%,[21] there are likely to be patients in the subgroup “without DM” who have subclinical or undiagnosed DM, as evidenced by some above-normal HbA1c in this cohort. Lastly, as this study is retrospective in nature, we cannot infer recommendations regarding optimal glycemic control management strategies in patients with advanced HF.

Acknowledgments

Funding Sources: Dr. Horwich was supported by NHLBI / NIH 1K23HL085097.

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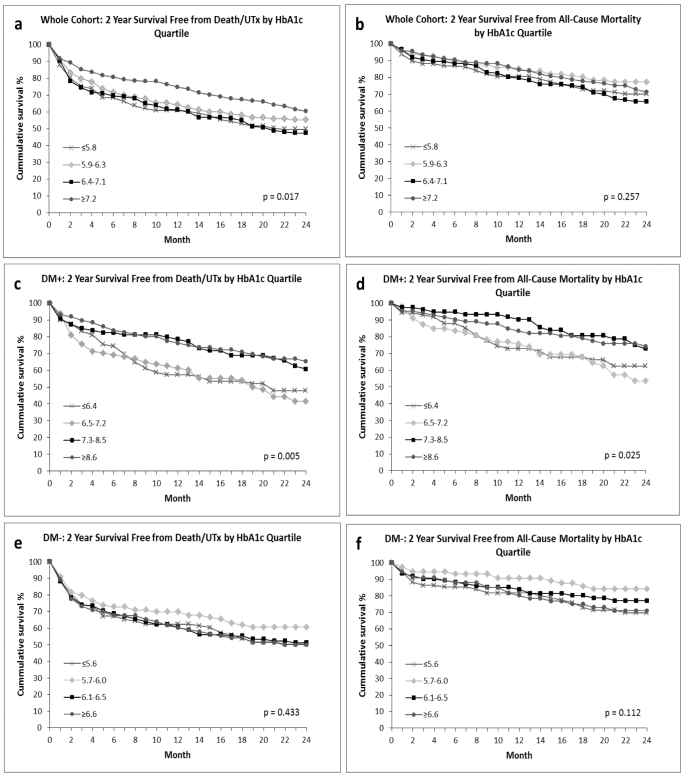

Figure 1.

Survival outcomes of advanced heart failure patients by HbA1c Quartiles. 1a. Whole Cohort: 2 Year Survival Free from Death/UTx by HbA1c Quartile (Q1 49.6%, Q2 55.3%, Q3 47.5%, Q4 60.4%) 1b. Whole Cohort: 2 Year Survival Free from All-Cause Mortality by HbA1c Quartile (Q1 70.2%, Q2 77.3%, Q3 65.7%, Q4 71.2%) 1c. DM+: 2 Year Survival Free from Death/UTx by HbA1c Quartile (Q1 47.9%, Q2 41.5%, Q3 60.7%, Q4 65.3%) 1d. DM+: 2 Year Survival Free from All-Cause Mortality by HbA1c Quartile (Q1 62.5%, Q2 53.5%, Q3 72.9%, Q4 74.4%) 1e. DM−: 2 Year Survival Free from Death/UTx by HbA1c Quartile (Q1 50.4%, Q2 60.6%, Q3 51.1%, Q4 49.9%) 1f. DM−: 2 Year Survival Free from All-Cause Mortality by HbA1c (Q1 69.8%, Q2 84.2%, Q3 77.1%, Q4 71.1%)

Table 1

HbA1c Quartiles by Subgroup

		Diabetes Mellitus	
Quartile	**Whole Cohort**	**Yes**	**No**
1	≤**5.8** (n=221)	≤**6.4** (n=90)	≤**5.6** (n=130)
2	**5.9–6.3** (n=205)	**6.5–.2** (n=94)	**5.7–6.0** (n=120)
3	**6.4–7.1** (n=213)	**7.3–8.5** (n=86)	**6.1–6.5** (n=143)
4	≥**7.2** (n=206)	≥**8.6** (n=88)	≥**6.6** (n=94)

Table 2

Baseline Characteristics by Subgroup

	Diabetes Mellitus		
Variable	**Yes**	**NO**	**P-value**
Age(years)	57.3 ± 10.4	53.0 ± 13.5	<0.001
Female	28.5%	27.1%	0.671
Myocardial ischemic etiology	59.2%	33.3%	<0.001
Hemoglobin A1c (%)	7.6 ± 1.7	6.0 ± 0.6	<0.001
Body mass index (kg/m2)	28.6 ± 5.4	26.5 ± 5.7	<0.001
New York Heart Association I–II / III–IV	25.3% / 74.7%	17.9% / 82.1%	0.030
Left ventricle ejection fraction(%)	25.3 ± 9.6	25.3 ± 13.0	0.946
Left ventricular end-diastolic diameter index (mm/m2)	33.6 ± 9.2	35.6 ± 11.5	0.020
Peak oxygen consumption(L/kg/min)	11.6 ± 3.5	13.5 ± 4.8	<0.001
Heart rate (bpm)	80.9 ± 15.5	81.6 ± 17.2	0.566
Mean blood pressure (mmHg)	80.7 ± 13.5	77.9 ± 12.4	0.004
Systolic blood pressure (mmHg)	111.5 ± 21.0	104.0 ± 18.1	<0.001
Pulmonary capillary wedge (mmHg) (n=560)	22.3 ± 8.1	21.6 ± 8.5	0.305
Hemoglobin (mL/g)	12.7 ± 2.1	13.2 ± 2.5	0.006
Creatinine(mg/dL)	1.6 ± 1.7	1.4 ± 1.4	0.092
Blood urea nitrogen(mg/dL)	34.8 ± 24.4	27.8 ± 18.1	<0.001
B-type natriuretic peptide (pg/dL)	597 (253 – 1300)	570 (216 – 1410)	0.876
Total cholesterol(mg/dL)	154.0 ± 58.2	147.6 ± 50.0	0.105
Cardiac resynchronization therapy	31.2%	40.6%	0.005
Implantable cardioverter defibrillator placement	63.3%	67.1%	0.253
Heart Failure Medications			
Beta blocker	83.8%	81.3%	0.349
Aldosterone antagonist	58.1%	59.5%	0.673
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker	83.8%	76.8%	0.012
Outcomes			
Death / Urgent transplantation 2 year	42.7%	42.7%	0.994
All-cause mortality 2 year	26.5%	17.4%	0.001

Table 3

Baseline Characteristics of the Cohort Stratified by Hemoglobin A1c Quartile

	Hemoglobin A1e Level (%)				
Variable	**≤ 5.8**	**5.9 – 6.3**	**6.4 – 7.1**	**≥ 7.2**	**P-value**
Age (years)	51.9 ± 12.8	55.1 ± 13.3	57.0 ± 12.2	55.6 ± 10.9	<0.001
Female	32.6%	25.4%	26.9%	25.4%	0.283
Myocardial ischemic etiology	38.9%	40.5%	41.1%	57.3%	<0.001
Body mass index (kg/m2)	26.6± 6.2	26.6± 5.3	27.1± 5.2	29.4± 5.6	<0.001
New York Heart Association I / II / III / IV	6.4% / 20.4% / 38.9% / 34.3%	2.5% / 20.8% / 50.9% / 25.8%	5.2% / 14.2% / 46.4% / 34.2%	2.7% / 16.3% / 44.9% / 36.1%	0.198
History of Diabetes Mellitus	17.6%	20.5%	43.0%	90.3%	<0.001
Left ventricle ejection fraction (%)	27.5 ± 14.1	24.9 ± 11.9	23.9 ± 11.4	25.0 ± 8.6	0.028
Left ventricular end-diastolic diameter index (mm/m2)	36.1 ± 11.6	36.5 ± 12.0	34.4 ± 9.5	31.9 ± 8.4	<0.001
Peak oxygen consumption (L/kg/min)	13.5 ±4.2	13.1 ± 5.0	12.4 ± 4.3	11.6 ± 3.8	0.014
Heart rate (bpm)	83.5 ± 18.8	81.2 ± 17.6	83.6 ± 15.6	81.5 ± 15.8	0.391
Mean blood pressure (mmHG)	77.0 ± 12.6	75.8 ± 11.5	74.9 ± 11.6	81.3 ± 14.4	<0.001
Systolic blood pressure (mmHG)	104.7 ± 17.4	105.7 ± 17.1	103.9 ± 19.2	114.6 ± 22.7	<0.001
Pulmonary capillary wedge (mmHG) (n=560)	20.8 ± 8.6	21.5 ± 8.2	22.6 ± 8.3	22.6 ± 8.1	0.173
Hemoglobin (mL/g)	12.7 ± 3.1	13.2 ± 2.0	13.1 ± 2.1	13.0 ± 2.0	0.127
Creatinine (mg/dL)	1.5 ± 1.2	1.4 ± 0.8	1.6 ± 1.7	1.7 ± 2.1	0.296
Blood urea nitrogen (mg/dL)	26.1 ± 16.1	28.1 ± 17.1	33.6 ± 22.9	35.7 ± 26.2	<0.001
B-type natriuretic peptide (pg/dL)	447 (179.7–240.0)	520.5 (240.5–1277.5)	706.0 (316.5–625.0)	588.0 (251.0–1300.0)	0.012
Total cholesterol (mg/dL)	152.3 ± 54.8	147.4 ± 47.4	144.9 ± 50.4	156.7 ± 60.1	0.110
Low-density lipoprotein cholesterol(mg/dL)	88.3 ± 40.0	83.5 ± 35.2	83.5 ± 35.0	85.4 ± 41.8	0.577
High-density lipoprotein cholesterol(mg/dL)	38.5 ± 16.5	36.2 ± 12.5	37.7 ± 16.2	35.7 ± 13.8	0.237
Triglycerides (mg/dL)	104.0 (69.5–164.5)	111.0 (77.0–180.0)	102.0 (71.0–146.0)	127.0 (76.0–257.0)	0.001
Heart Failure Medications					
Beta blocker	76.9%	83.9%	82.7%	86.4%	0.066
Aldosterone antagonist	52.5%	62.4%	59.3%	62.1%	0.126
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker	73.3%	79.5%	80.8%	85.9%	0.013

Table 4

Baseline Characteristics of the Diabetic Subgroup Stratified by Hemoglobin A1c Quartile

	Hemoglobin A1c Level (%)				
Variable	**≤ 6.4**	**6.5–7.2**	**7.3–8.5**	**≥ 8.6**	**P-value**
Age (years)	58.6 ± 9.6	59.0 ± 10.1	58.0 ± 10.9	53.7 ± 10.0	0.001
Female	28.9%	29.3%	24.4%	31.0%	0.797
Myocardial ischemic etiology	61.1%	58.5%	67.4%	50.0%	0.130
Body mass index (kg/m2)	27.5 ± 5.1	27.8 ± 5.2	28.6 ± 5.1	30.7 ± 5.9	<0.001
New York Heart Association I / II / III / IV	2.9% / 17.4% / 43.4% / 36.2%	4.3% / 10.1% / 47.8% / 37.7%	3.3% / 11.5% / 54.1% / 31.1%	1.6% / 20.6% / 38.1% / 39.7%	0.678
Hemoglobin A1c (%)	5.8 ± 0.4	6.8 ± 0.2	7.9 ± 0.4	10.0± 1.3	<0.001
Left ventricle ejection fraction (%)	26.4 ± 10.5	24.5 ± 10.7	24.5 ± 8.4	25.5 ± 8.5	0.501
Left ventricular end-diastolic diameter index (mm/m2)	35.5 ± 11.0	35.1 ± 8.8	32.7 ± 8.3	30.8 ± 8.0	0.014
Peak oxygen consumption (L/kg/min)	11.9 ± 2.7	11.1 ± 3.6	11.6 ± 3.3	11.8 ± 4.1	0.692
Heart rate (bpm)	79.7 ± 16.0	78.4 ± 15.1	82.5 ± 15.9	82.9 ± 14.7	0.213
Mean blood pressure (mmHg)	76.4 ± 12.1	77.5 ± 12.1	83.9± 13.1	85.2 ± 14.7	<0.001
Systolic blood pressure (mmHg)	107.2 ± 16.6	107.0 ± 20.1	115.4 ± 21.1	116.6 ± 24.2	0.003
Pulmonary capillary wedge (mmHg) (n=560)	21.4 ± 7.5	22.5 ± 8.6	22.6 ± 7.6	22.7 ± 8.8	0.801
Hemoglobin (mL/g)	12.2 ± 2.3	12.8 ± 2.1	12.9 ± 1.9	13.0 ± 1.9	0.096
Creatinine (mg/dL)	1.5 ± 0.8	1.5 ± 0.8	1.8 ± 2.6	1.6 ± 1.8	0.540
Blood urea nitrogen (mg/dL)	30.1 ± 18.0	35.9 ± 23.8	41.7 ± 32.8	31.8 ± 19.1	0.008
B-type natriuretic peptide (pg/dL)	654.0 (255.0–1300.0)	516.0 (252.0–1220.0)	743.0 (340.0–1301.0)	503.0 (202.5–1055.0)	0.557
Total cholesterol (mg/dL)	151.2 ± 56.1	148.2 ± 52.8	155.9 ± 64.1	161.1 ± 60.0	0.507
Low-density lipoprotein cholesterol(mg/dL)	83.9 ± 44.0	83.8 ± 33.1	81.5 ± 38.8	90.4 ± 45.3	0.575
High-density lipoprotein cholesterol(mg/dL)	35.3 ± 11.7	37.6 ± 16.3	33.8 ± 9.6	37.4 ± 15.5	0.266
Triglycerides (mg/dL)	116.0 (84.0–188.0)	102.0 (65.0–140.0)	126.0 (75.0–273.0)	139.0 (81.0–248.0)	0.029
Heart Failure Medications					
Beta blocker	80.0%	81.9%	84.9%	88.6%	0.425
Aldosterone antagonist	53.3%	59.6%	60.5%	59.1%	0.763
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker	83.3%	81.9%	79.1%	90.9%	0.175
Anti-Diabetic Medications					

	Hemoglobin A1c Level (%)				
Variable	**≤ 6.4**	**6.5–7.2**	**7.3–8.5**	**≥ 8.6**	**P-value**
Insulin	33.3%	21.4%	35.2%	48.9%	0.003
Sulfonylureas	25.0%	23.8%	30.7%	42.2%	0.033
Glitazones	8.3%	5.1%	14.8%	15.4%	0.276
Metformin	8.3%	37.5%	20.5%	26.6%	0.019

Table 5

Baseline Characteristics of the Non-Diabetic Subgroup Stratified by Hemoglobin A1c Quartile

	Hemoglobin A1c Level (%)				P-value
	≤ 5.6	5.7–6.0	6.1–6.5	≥ 6.6	
Age (years)	50.1 ± 14.0	53.9 ± 13.4	54.1 ± 13.7	54.2 ± 12.4	0.038
Female	30.8%	28.3%	26.2%	21.7%	0.500
Myocardial ischemic etiology	35.4%	35.0%	34.3%	26.6%	0.499
Body mass index (kg/m2)	26.2 ± 6.6	26.9 ± 5.3	26.4 ± 5.9	26.6 ± 4.7	0.807
New York Heart Association I / II / III / IV	6.7% / 21.3% / 38.2% / 33.7%	5.9% / 22.4% / 42.4% / 29.4%	3.5% / 19.1% / 52.2% / 25.2%	4.5% / 17.9% / 44.8% / 32.8%	0.783
Hemoglobin A1c (%)	5.3 ± 0.3	5.9 ± 0.1	6.3 ± 0.1	6.9 ± 0.3	<0.001
Left ventricle ejection fraction (%)	27.8 ± 14.5	26.8 ± 14.3	23.1 ± 11.1	23.4± 11.1	0.009
Left ventricular end-diastolic diameter index (mm/m2)	36.7 ± 12.8	34.7 ± 9.0	36.4 ± 12.9	34.3 ± 10.3	0.380
Peak oxygen consumption (L/kg/min)	13.8 ± 4.1	13.5 ± 5.1	13.4 ± 5.5	13.4 ± 4.4	0.968
Heart rate (bpm)	84.3 ± 20.2	78.3 ± 15.5	82.3 ± 16.5	81.3 ± 15.7	0.107
Mean blood pressure (mmHG)	76.3 ± 11.7	79.1 ± 12.9	79.1 ± 12.2	76.8 ± 12.7	0.208
Systolic blood pressure (mmHg)	103.2 ± 16.5	105.8 ± 17.3	104.8 ± 18.0	101.9 ± 20.7	0.476
Pulmonary capillary wedge (mmHg) (n=560)	20.1 ± 9.3	21.6 ± 7.9	21.8 ± 8.3	22.9 ± 8.3	0.257
Hemoglobin (mL/g)	12.6 ± 2.2	13.4 ± 3.6	13.4 ± 1.9	13.4 ± 2.1	0.040
Creatinine (mg/dL)	1.5 ± 1.4	1.3 ± 0.9	1.5 ± 0.8	1.6 ± 2.4	0.656
Blood urea nitrogen (mg/dL)	24.7 ± 15.3	25.9 ± 17.7	30.4 ± 19.5	30.8 ± 19.2	0.017
B-type natriuretic peptide (pg/dL)	386.0 (135.0–1093.0)	402.0 (185.0–838.5)	687.0 (371.0–1610.0)	1020.0 (477.0–2150.0)	<0.001
Total cholesterol (mg/dL)	148.8 ± 49.4	152.1 ± 52.3	143.2 ± 47.0	146.5 ± 50.0	0.557
Low-density lipoprotein cholesterol (mg/dL)	87.4 ± 36.3	87.1 ± 36.4	81.7 ± 35.1	85.8 ± 37.8	0.606
High-density lipoprotein cholesterol (mg/dL)	38.3 ± 15.8	39.0 ± 16.0	36.8 ± 14.9	36.5 ± 16.2	0.584
Triglycerides (mg/dL)	92 (69 – 141)	108 (75 – 174)	96 (69–142)	105 (79 – 170)	0.236
Heart Failure Medications					
Beta blocker	76.9%	80.0%	82.5%	87.2%	0.252
Aldosterone antagonist	53.8%	56.7%	64.3%	63.8%	0.236
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker	70.0%	74.2%	79.0%	86.3%	0.031